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THE USE OF GOLD SALTS IN THE TREATMENT OF EXPERIMENTAL TUBERCULOSIS IN GUINEA-PIGS

XVIII. STUDIES ON THE BIOCHEMISTRY AND CHEMOTHERAPY OF TUBERCULOSIS

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The use of gold in therapy is by no means new and a complete survey of the history and literature has been impracticable. The earliest reference which I have found in the literature states that Abu Moussa Djafar or Geber, surnamed the Wise, who was born at Houran in Mesopotamia in the middle of the 8th century, recommended the use of gold as a cure for every disease of men, animals and plants, asserting that all the metals were diseased except gold.

Sprengel's *Arzneikunde* (1800) in the chapter on Medical Culture among the Arabians, refers to the many medical and philosophical treatises of Ebn Sina (better known as Avicenna) who lived from 978-1036 A. D. This ancient philosopher recommended gold, silver and other metals for internal use as blood purifiers. Gold foil was also used in his time to coat pills in the belief that the gold coating increased their efficacy.

Naturally the alchemists in their eager interest in gold did not neglect its use in medicine and Paracelsus (1493-1541), the alchemist and chemist who insisted that the true use of chemistry was to make medicines rather than gold, considered gold as a specific in all affections of the heart; he based this belief on the fact that in the mystic scale, gold is in harmony with that viscus. The Paracelsian "Elixir of Life" or panacea for all ills was said to be composed of gold and mercury. The so-called potable gold or liquid gold and its use in medicine dates from this same period and was highly recommended by Roger Bacon and many others. The Sceptical Chymist (Boyle) criticises its use but admits some wonderful cures. In 1540, Lecoque is said to have cured syphilis by the use of gold, which was much like mercury in its action. Hahnemann ascribed great curative power to gold and Burnett recommended trituration of gold leaf 1:1,000,000 as a heart tonic.

The use of gold as a cure for alcoholism was long exploited under the name of the Keeley Gold Cure but in 1891 it was confessed that the remedy used contained no gold and that the name was used with fraudulent intent.

In 1917, Marsalongo and Vivaldi reported 32 cases of typhoid and paratyphoid fever successfully treated with colloidal gold. At different times and by different workers, gold has been used in the treatment of syphilis, heart disease, cancer, chronic Bright's disease, typhoid fever, and chronic rheumatism.

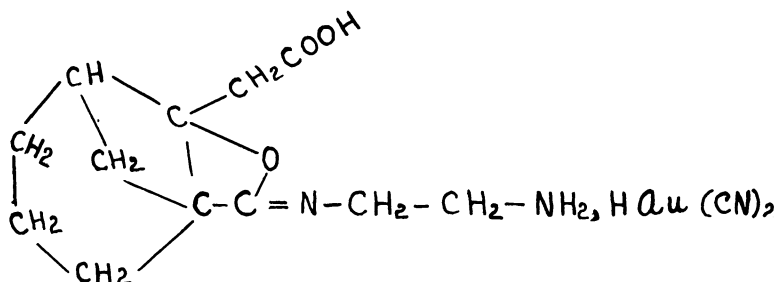
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It is also said to have a special influence on the lithemic and fatty degenerations, and on various spinal and cerebral sclerosis.

The use of gold in the treatment of tuberculosis, according to White, dates from the time of Paracelsus; for many years after his time, gold in combination with mercury was depended on in the treatment of the cachexias resulting from phthisis, scrofula, syphilis, etc. After a time, however, some serious accidents led to a discontinuance of its use until 1810 when Chrestien brought it back into prominence. In 1890, Robert Koch stated that gold cyanid completely inhibits the growth of tubercle bacilli in dilution of 1:2,000,000 but that it is entirely without influence in the animal body. In 1891, J. B. White recommended the use of double chlorid of sodium and gold combined with iodid of manganese in the treatment of tuberculosis. The effects noted were a distinct prolongation of life in animals, and in human patients gain in weight and appetite, diminution of cough and sputum and râles, absorption of abnormal deposits, and improvement of blood conditions. Merrill also used White's treatment on 20 patients for 2 years and considers its value unquestionable. In 1891 also, the well known Gibbes and Shurley treatment for tuberculosis was published. This consisted of a preliminary iodine treatment for 2 weeks, then double chlorid of gold and sodium for 10 days, then again the iodine, and so on, the 2 treatments alternating. During the time of the treatment, inhalation of chlorine gas was recommended. They reported about 50% of their cases "practically cured."

The next and the most extended group of experiments on the use of gold salts in tuberculosis were published between 1912 and 1915 by a number of German investigators. Several workers reported results from the use of gold potassium cyanid especially in tuberculosis of the skin. Meyer reports good results in general tuberculosis, especially if the gold salt is combined with some substance like borcholin which is said to dissolve the fatty sheath of the tubercle bacillus. Oberstadt reported good influence on the skin lesions, but no case of perfect recovery. He thinks the effect is produced more rapidly if tuberculin treatment is combined with the treatment with the gold salt. Bruck and Glück, after a series of rather unsuccessful experiments in guinea-pigs, used gold potassium cyanid in the treatment of lupus. They ascribed their failure in guinea-pigs to the fact that the gold salt needs to be injected intravenously at frequent intervals and frequent intravenous injections are impracticable in guinea-pigs. Bettmann obtained similar results in the same type of cases. Junker reports good effects from the use of gold salts in pulmonary as well as in skin tuberculosis in patients. Rosenthal injected gold tricyanid directly into the diseased area in men, claiming good results. Poor and Geber also report success from the use of gold potassium cyanid in patients having skin tuberculosis. A series of 7 or more papers, published by Spiess and Feldt, together or separately, between 1912 and 1916, form the most extensive contribution to the literature on the treatment of tuberculosis by means of different salts of gold. These authors consider gold cyanid and gold potassium cyanid too toxic for use in human patients. As cantharidin had earlier been found to have a marked affinity for tuberculous tissues, they conceived the idea of reducing the toxicity of the cantharidin and using it as a carrier for the specific gold cyanid. They were able to reduce the toxicity of the cantharidin 700 times without altering its affinity for tubercles by condensing it with ethylenediamin. This compound was quite nontoxic and combined

readily with gold cyanid. They used first the auric salts but found them 100-1,000 times less efficacious than the aurous salt and therefore in all their later work they used mono-canthalidyl-ethylenediamin-aurous-cyanid, the formula of which they give as follows:



The compound was first tested on about 100 animals during 1½ years and was then used on human patients. They claim that its effects are due partly to a direct inhibitory action on the tubercle bacilli and partly to an indirect action on the defensive agencies of the body. It stimulates connective tissue formation and destroys disease products by its oxidizing power. In experimental tuberculosis in animals, they claim that weight was increased and life was prolonged and tubercles were replaced by scar tissue, especially in rabbits. In guinea-pigs, the effects were not so marked, a fact which they attribute to the necessity of administering the drug subcutaneously. Long continued subcutaneous treatment causes necrosis, and the development of gold tolerance. This was shown in vitro, as, after 1½ months, the bacilli grew on mediums containing 1 part of gold cyanid to 400,000 parts of agar, whereas at first they would not develop in a dilution of 1 part in 2,000,000.

In contrast to the above favorable reports on the use of gold salts in tuberculosis, Koch in 1890 stated that the gold salts were without effect in animals. Perutz and Seppel, Walther, and Schoenfeld admitted that they obtained good results at first, especially in early cases, but stated that these results were transient and did not interfere with the progress of the disease. Blendberger, even in cases of lupus, was unable to obtain results at all comparable to those reported by other workers. Pekanovich, Hauck, and Pasini all call attention to the dangers from the use of gold cyanids, since they are, according to Hauck, severe blood poisons, reducing the number of both red and white cells and causing a severe hemolytic icterus. Pekanovich also reported severe hemorrhages after their use.

On the physiologic and pharmacologic action of gold salts in the animal body, much has been written and it will not be practicable to review more than a few of the most important communications having special reference to the use of gold in tuberculosis. Pereira's *materia medica* of 1839 states that "its effects are similar to those of mercury. Its salts are corrosive, but less so than mercuric chlorid. In small doses, they are stimulant, promoting the secretion of skin glands, salivary glands and kidneys. In doses of 0.1 gm. in man, they may cause fever, a reaction which Chrestien considered necessary for curative effect. Within proper dosage, no ill effects are produced." Heubner says that the rapidly fatal dose of sodium-gold chlorid is 15 mg. of the salt per kg. of body weight or 7 mg. of gold. If such a dose is given, the blood pressure falls rapidly until it reaches 0 and the animal dies in a few minutes of respiratory

stasis, all the organs showing hyperemia, with occasional ecchymoses and larger hemorrhages. All the veins and capillaries are greatly dilated and often ruptured while the arteries are strongly contracted. In other words, Heubner regards gold salts as vascular poisons. A more chronic intoxication is also described by Heubner. By injecting very slowly and thus avoiding a certain concentration in the blood, more than the acutely fatal dose can be introduced without causing immediate death. In these chronic intoxications, there is no indication of capillary poisoning and no macroscopic change in the organs. Microscopically, the kidney presents the usual picture of metallic poisoning—hyperemia, epithelial degeneration, fat cylinders in the tubules. The lungs show areas of hepatization, and the smaller bronchi are closed by hyaline masses. Many pigmented granular cells are seen. Heubner was unable to find gold microscopically in the organs. Richards, working in Heubner's laboratory, reported finding metallic gold in the nuclei of many organ cells, a report which Heubner failed to corroborate. By chemical analysis, however, Heubner found gold in the blood one half hour after intravenous injection, in the liver, spleen, lungs, and kidneys. Hauck states that gold cyanids cause a great diminution of the erythrocytes and leukocytes in the blood with a severe hemolytic icterus. Junker also notes a rapid lowering of the hemoglobin content of the blood. Bruck and Glück, on the other hand, found no effect on the blood from the use of gold cyanids. Schumacher states that the gold cyanids quickly break down in the body and form probably gold protein compounds which soon release colloidal gold. As the cyanid group is soon synthesized to the nontoxic sulphocyanid or rhodanid, Schumacher thinks that the effects in the body both toxic and therapeutic are due to the colloidal gold and not to the cyanid radicle. Spiess and Feldt and others who are using the gold cyanid in the treatment of tuberculosis admit that hyperemias and hemorrhages result from their use but insist that these are confined to the tuberculous areas, resembling the tuberculin reaction and leading to healing. Colloidal gold solutions have also been injected intravenously. Busquet states that colloidal gold raises the blood pressure and increases the force of the heart beats, diminishing their number, while soluble gold salts have a quite opposite effect, lowering the blood pressure, increasing the frequency of heart beats and diminishing their amplitude.

Koch found that gold in the form of cyanids had very little bactericidal effect on the tubercle bacillus but completely inhibited its growth in a dilution of 1:2,000,000. This statement was verified by Rosenthal and by Behring for other bacteria. Behring, however, found that this high inhibitory power in water solutions was reduced in blood serum to 1:20,000-30,000. Feldt demonstrated that colloidal gold had an inhibitory effect nearly equal to that of gold cyanid, completely inhibiting the growth of tubercle bacilli in a dilution of 1:1,000,000. He also found that gelatin mediums containing 1 part of colloidal gold in 6,000 parts of gelatin remained sterile though left open for 45 days, while control tubes containing no gold were covered in 3 days with a growth of air organisms.

My own experiments on the bactericidal and inhibitory power of gold salts on tubercle bacilli correspond entirely with the findings of

Koch and Behring. DeWitt and Sherman reported that 1 part in 1,000 of gold chlorid is required to kill tubercle bacilli while 1% solutions of gold tricyanid were not always able to kill all the organisms. As opposed to this low bactericidal power, I have found that 1 part in 2,000,000 is able to inhibit completely the growth of these organisms in the test tube. On the other hand, I have found a certain tolerance develop very slowly. After 4 months' growth on agar containing gold, the bacilli would grow very well on mediums containing 1 part of gold in the form of gold potassium cyanid in 2,000,000 and slightly on tubes containing 1 part in 1,000,000. This is not nearly so marked a tolerance as was described by Feldt who states that after 11½ months, he obtained a good growth on dilutions of 1 part of gold cyanid in 400,000 of the mediums. Shiga, on the other hand, asserts that in his experiments the tubercle bacilli developed no tolerance toward gold potassium cyanid. The question of acquired tolerance is one of considerable importance in the chemotherapy of a disease like tuberculosis in which treatment must be continued for long periods. According to our results in the *in vitro* experiments, however, the tolerance of the tubercle bacillus to gold develops so slowly as not to be a very important factor in the consideration of the treatment of tuberculosis with gold.

The stimulation of the growth of tubercle bacilli by solutions of gold too dilute to kill or inhibit is another important consideration in the use of gold in chemotherapy. We have frequently noticed in our culture tubes that the higher dilutions contained a more luxuriant growth than the control tubes. Takenaka reported that gold salts in broth dilution gave the following results:

- 1: 100,000,000 caused stimulation at first.
- 1: 10,000,000 caused no inhibition and no stimulation.
- 1: 2,000,000 caused no inhibition and no stimulation.
- 1: 1,000,000 caused no inhibition but often stimulation.
- 1: 500,000 caused no inhibition.
- 1: 100,000 caused marked inhibition.

The importance of the consideration of stimulation of growth by a gold concentration below that required to inhibit the growth may easily be appreciated, since it is difficult to keep the concentration of gold in the animal body constantly at or above the point required for inhibition.

My own experiments began Jan. 26, 1915. Eighteen guinea-pigs were inoculated subcutaneously with a strain of human tubercle bacilli of fairly low virulence, the untreated controls dying of generalized

tuberculosis in from 4-10 months. Ten days after inoculation, treatment with gold salts was begun, partly by subcutaneous injection and partly by feeding. Aug. 25, 1915, Sept. 14, 1915, Nov. 17, 1915 and Dec. 6, 1915, and Feb. 28, 1916, other sets were inoculated and treated with gold salts. In most cases, treatment was begun 24 hours after inoculation. In these experiments, some animals were treated with auric cyanid, some with gold potassium cyanid and some with aurous cyanid. All were fed daily and all received injections once or twice a week, sometimes intracardiac and sometimes subcutaneous or intramuscular. The subcutaneous injections often caused ulceration and necrosis of the surrounding tissues; the intramuscular injections of oil emulsions resulted in infiltration of the muscles from the slow absorption, with stiffness, lameness and paralysis. The intracardiac injections were not entirely without danger and a number of animals died immediately after the injection either from hemorrhage or from the toxic effects of the gold cyanids. In many cases, as many as 16 or 18 heart injections were given to the same animals.

Later, desiring to try the effect of the cantharidyl-ethylenediamin-aurous-cyanid recommended by Spiess and Feldt, and being unable to procure any on account of the war, I had some made in my laboratory according to the directions given in the German patent. This preparation was used in the treatment of about 30 tuberculous guinea-pigs. At first it was introduced by intracardiac injection, but later, having found by chemical analysis that it was quickly and completely absorbed from the subcutaneous tissue, the less dangerous method of subcutaneous injection was used. This preparation is much less toxic than the simple cyanids and caused no necrosis in the skin and subcutaneous tissue. Its power of inhibition, however, was somewhat less as the highest dilution which completely inhibited growth of the tubercle bacillus in the test tube was 1 part of gold in the form of auro-cantan to 250,000 parts of agar instead of 1 part of gold to 2,000,000 parts of agar.

Having determined that in 1 week from 40-50% of the amount of gold introduced was excreted through the urine and feces, injections were made once a week to keep the concentration in the organism high enough to equal the level necessary for inhibition of the growth of the tubercle bacillus. The dose used at first was usually 2 mg. This was soon increased to 4 mg. and later to 5, then 8, and then 10 mg. of the preparation, about 40% of which is gold. If we could believe that this gold is uniformly distributed throughout the body and retains in the

body an inhibitory power equal to that which it possesses in the test tube, these doses repeated at intervals of 1 week would constantly maintain a concentration sufficient to prevent the growth of any tubercle bacilli in the body. Table 1 will show that this hope was not realized. The total amount of gold administered and the length of life of the animals, as well as the extent of the disease are indicated in the table and are compared with the length of life and extent of the

TABLE 1
A SUMMARY OF THE EFFECT OF TREATMENT WITH GOLD SALTS ON THE PROGRESS OF
TUBERCULOSIS IN GUINEA-PIGS

Animals Treated with Gold								
Gold Salt	Mg. Gold	Days of Life	Local Glands	General Glands	Extent of Disease in			Notes
					Liver	Spleen	Lungs	
AuK(CN) ₂	54.40	64	—	—	++	+++	+++	Pericarditis
AuK(CN) ₂	92.48	77	+++	—	+++	+++	+++	
AuK(CN) ₂	92.48	77	+++	+++	+++	+++	+++	
AuK(CN) ₂	261.80	115	+++	+++	+++	+++	+++	
AuK(CN) ₂	184.96	120	+++	—	+++	+++	+++	
AuK(CN) ₂	178.84	125	+++	+++	+++	+++	+++	
AuK(CN) ₂	189.72	134	+++	+++	+	++	+	
Au(CN) ₃	145.55	101	+	—	+++	+++	—	
Au(CN) ₃	211.58	132	+++	+++	+++	+++	+++	
Au(CN) ₃	209.45	135	+	+	+	+++	+	
Au(CN) ₃	237.85	150	+	—	+	+++	+++	
Au(CN) ₃	249.92	160	+++	—	+++	+++	+++	
Au(CN) ₃	130.64	177	+++	+++	+++	+++	+++	
Au(CN) ₃	309.56	188	+	—	+++	+++	+++	
Au(CN) ₃	173.24	211	+++	+++	+++	+++	+++	
AuCN	35.20	44	+	—	—	+	—	
AuCN	35.20	49	+	+	—	+	—	
AuCN	97.68	197	+++	+++	+++	+++	+++	
AuCN	129.36	237	+++	+++	+	+++	+++	
Aurocantan	1.6	7	++	+	—	—	—	Hemorrhage Acute infec.
Aurocantan	0.53	9	—	—	—	—	—	
Aurocantan	2.4	17	—	—	—	—	—	Hemorrhage
Aurocantan	9.6	37	+++	+++	+++	+++	+++	
Aurocantan	4.8	42	+	—	—	—	—	Killed Hemorrhage
Aurocantan	13.6	51	+++	++	+++	++	+++	
Aurocantan	13.6	57	+++	+++	+++	+++	+++	Killed Hemorrhage
Aurocantan	14.4	60	—	—	—	+++	+++	
Aurocantan	5.06	68	++	+++	—	+	—	Hemorrhage
Aurocantan	28.0	90	+++	+++	+++	+++	+++	
Aurocantan	16.8	107	+	—	—	+++	+++	Hemorrhage
Aurocantan	8.5	115	+	+	+	+	—	
Aurocantan	12.26	153	+	+	—	—	—	Killed Killed Killed
Aurocantan	31.6	160	+	+	—	—	—	
Aurocantan	15.06	181	+	++	—	+++	++	Pneumonia Pneumonia Pneumonia
Aurocantan	11.46	184	+	+++	++	+++	+++	
Aurocantan	90.8	227	+	+	+	+	—	Pneumonia Pneumonia
Aurocantan	90.8	228	++	+++	+++	+	—	
Aurocantan	62.0	232	+	+	+	—	++	Pneumonia Pneumonia
Aurocantan	21.86	236	++	+++	+	+	++	
Aurocantan	17.06	242	+++	+++	+++	+++	+++	Pneumonia Pneumonia
Aurocantan	17.06	247	++	+++	+++	+++	+++	

TABLE 1
A SUMMARY OF THE EFFECT OF TREATMENT WITH GOLD SALTS ON THE PROGRESS OF
TUBERCULOSIS IN GUINEA-PIGS

Animals Not Gold Treated (Controls)						
Days of Life	Local Glands	General Glands	Extent of Disease in			Notes
			Liver	Spleen	Lungs	
57	+++	+++	+++	+++	+	Pericarditis; pneumonia Pericarditis
57	+++	+++	+++	+++	+	
62	+++	+++	+	++	+++	Pericarditis Hemorrhage
92	+++	+++	+++	+++	+++	
97	+++	++	++	++	+	
98	+++	+++	+++	+++	+++	
100	+++	+++	+++	+++	+++	Peritonitis Pericarditis Killed
105	+++	+++	+++	+	++	
120	+++	—	+++	+++	+++	
122	+++	+	+	+	++	
122	+	+	+++	+++	+++	Tuberculosis of omentum
133	+++	+++	+++	+++	+++	
143	+++	+++	+++	+++	+++	
147	+++	+++	+++	+++	+++	
167	+++	+++	+++	+++	+++	
174	+++	+++	+++	+++	+++	
176	+++	+++	+++	+++	+++	
180	+++	+++	+++	+++	+++	
181	+++	+++	+++	+++	+++	
184	+++	+++	+++	+++	+++	
197	+++	+++	+++	+++	+++	
238	+++	+++	+++	+++	+++	
243	++	—	+++	+++	+++	
264	+++	+++	+	+++	+++	
288	+++	+++	+++	+++	+++	
293	+++	+++	+++	+++	+++	
315	+++	+++	+++	+++	++	
27	+++	+++	—	+++	—	Hemorrhage Killed Killed Killed
45	—	—	—	+	+	
59	+++	+++	+++	+++	+++	
104	+++	+++	+++	+++	+++	
105	+++	+++	+++	+++	+++	
105	+	++	+++	+++	+++	
113	+	—	—	—	—	
142	—	—	—	—	—	
162	—	—	—	+++	+++	
206	+++	+++	++	+	—	
236	++	+	—	—	—	
237	+++	+++	+++	++	—	
285	+++	+	—	+++	+++	
299	+++	++	+++	+++	+	
299	+	—	—	—	—	
299	+	+	—	+	+	
321	+	—	—	—	—	

disease in untreated control animals which were inoculated in the same way and with the same dose of the same strain. In the earlier experiments, the strain of human tubercle bacilli used was of so low a virulence that some of the controls failed to develop the disease or showed only a slight development. Therefore, in later experiments, a much more virulent strain was used. In the table, "local glands" are the lymph glands near the point of inoculation, and the term "general glands" refers to lymph glands in other organs of the body. Absence

of evidence of tuberculosis in an organ is indicated by —, a small number of tubercles is indicated by +, while a very extensive process is shown by +++.

It may be seen from this table that the treatment with gold salts had no beneficial effect on the progress of tuberculosis in guinea-pigs. Life was not prolonged and the extent of the disease in the different organs was certainly not less marked in the treated than in the untreated animals. Indeed, if any distinction can be drawn, it will be in favor of the untreated control animals.

In order to determine whether the gold was well distributed throughout the animal body, my assistants Sidney M. Cadwell and Miss Gladys Leavell developed a method of analysis for the small amounts of gold found in the tissues and analyzed the tissues of a considerable number of animals, tuberculous and nontuberculous, which had been treated with the various gold salts. The details of this analytic work are presented in another paper which will soon be published.* Table 2,† however, presents figures obtained by averaging the amounts obtained in the various organs of all the different animals examined.

TABLE 2
DETAILS OF EXPERIMENTAL WORK TO DETERMINE THE DISTRIBUTION OF GOLD
THROUGHOUT THE ANIMAL BODY

Average	C ₄ N ₄ H ₄ Au		AuK(CN) ₂		Au(CN) ₃		AuCN	
	Treated	Control	Treated	Control	Treated	Control	Treated	Control
Days lived.....	130	218.6	101.7	161.5	155.5	161.5	132	161.5
Extent of disease....	60%	35%	95%	95%	95%	95%	95%	95%
Mg. gold received....	13.34		150.67		210.95		74.36	
Percentage								
gold excreted.....	40.82		17.55					
gold in organs.....	9.527		16.4		0.72		0.465	
gold in body.....	26.13		59.48					
Mg.								
found in liver.....	0.447		0.69		0.98		0.265	
found in spleen....	0.127		0.109		0.083		0.045	
found in lungs.....	0.071		0.168		0.105		0.12	
found in kidneys...	0.12		0.06		0.09		0.03	
found in lymph								
glands.....	0.053				0.02		0.09	
found in skin.....	0.45		0.27					
found in intestines	0.26		0.69					
found in blood.....	0.069							
found in body.....	4.08		4.68					
gold per gm.								
of liver.....	0.0212		0.078		0.027		0.007	
of spleen.....	0.0916		0.1645		0.0358		0.011	
of lungs.....	0.0105		0.0305		0.009		0.0085	
of kidneys.....	0.0263		0.0087		0.0165		0.007	
of lymph glands.	0.0246				0.005		0.027	
of heart.....	0.009							
of blood.....	0.006							
of skin.....	0.027		0.0247					
of intestines.....	0.0075		0.013					
of body.....	0.012		0.0145					

*Accepted for early publication in the Journal of Pharmacology.
†Reprinted from the American Review of Tuberculosis, 1917, 1, p. 424.

It will be seen from Table 2 that the gold is not uniformly distributed throughout the body, the spleen containing more per gm. weight of the organ than any of the other organs. This may be due to the fact that the spleen is the organ in which red blood cells are for the most part destroyed, and these may easily carry with them an excessive amount of gold. In cases in which the brain was examined, no gold was found in it, and usually none in the blood except for a very short time after injection. If we examine the amount of gold found per gm. weight of the organs, we can readily see that even the smallest concentrations are far greater than the 1:2,000,000 generally accepted as the concentration required to inhibit in the test tube the growth of tubercle bacilli, while the amount in the spleen at least is more than sufficient to equal the concentration 1:20,000-30,000 stated by Feldt to be sufficient for complete inhibition in blood serum. Yet the spleen is the organ earliest and most severely involved in the tuberculous process. It is difficult to explain the fact that gold salts are so ineffective in the body of the guinea-pig, although found there in concentrations more than sufficient to inhibit growth, unless we assume that in these organs the gold is fixed in the cells and no longer has the power to act on the bacilli.

The main pathologic lesions found in both tuberculous and non-tuberculous animals treated with gold salts are hyperemia of all the organs and fat infiltration of the liver and kidney. Hemorrhages were by no means uncommon, sometimes from the mesenteric vessels and sometimes from thoracic vessels. Frequent small hemorrhagic foci were found in the lungs and occasional hemorrhagic infarcts. In some cases I have noted zones of hemorrhage surrounding tubercles, but I have not found them so common as noted by Spiess and Feldt.

In reports on the efficacy of gold in the treatment of tuberculosis, as indeed is true of all other treatments of tuberculosis, we generally find the statements made that the treatment prolonged life, increased weight, caused scarring of tubercles, etc. Table 1 shows clearly that the duration of life in tuberculous guinea-pigs, whether treated or untreated is very variable, while Table 2 demonstrates that the average duration of life of the controls is greater than that of the treated animals. In any single series of animals, unless a very large dose of a very virulent culture is administered or unless intravenous inoculation is practiced, we will find certain animals living very much longer than the others, even though all received the same dose of the same culture. Thus in one series of guinea-pigs inoculated Jan. 26, 1915, one died May 26, another June 8, another June 23, another July 12, another

July 19, while one lived until Nov. 15, 1915. Lewis noted a similar lack of uniformity in the duration of life in sets of animals receiving the same inoculation. Hence we may say that prolongation of life, unless it is consistent and marked, cannot be taken as an index of the value of any therapeutic agent. As to the weights, it is stated that the controls constantly diminished in weight while the treated animals increased. My experience has been that, unless a massive and overpowering injection is given, practically all animals will increase in weight for a time, beginning to diminish in weight only when the disease has progressed to the point where general intoxication is overpowering the animal and death is imminent. The question of weight, then, depends on dose and virulence of the organism rather than on treatment.

TABLE 3
DAYS OF LIFE AND WEIGHTS OF A SET OF GUINEA-PIGS GIVEN LARGE DOSE OF
VIRULENT TUBERCLE BACILLI

	Treated with Aueroantant					Controls				
	1	2	3	4	5	1	2	3	4	5
Days of life.....	92	51	57	37	7	105	105	27	104	59
Weight, gm.:										
1st week	530	615	525	240	355	580	730	590	295	240
2nd week	520	585	500	230		620	720	650	315	240
5th week	530	615	505	260		625	675	680	335	260
7th week	520	595	510	230		650	630	660	315	240
9th week	520	595	565	230		670	640		355	280
11th week	475	585	555	225		645	645		365	285
13th week	465	585	575			670	645		385	290
15th week	445	580				685	645		403	257
17th week		545				630	510		395	205
21st week		560				635	580		410	
23rd week		525				655	560		430	
25th week		495				650	570		385	
27th week		445				675	570		360	
29th week						610	500			

Table 3 gives the days of life and the weights throughout life of a set of guinea-pigs which received a rather large dose of a virulent culture of human tubercle bacilli. In this set the weights were more irregular and diminished more than with smaller doses of less virulent organisms. Even in this set, the weights, as well as the duration of life were better in the controls than in the treated animals. Furthermore, I have never seen any tendency to connective tissue encapsulation or scarring of tubercles such as is described by many writers.

From my experiments then, the conclusion must be drawn that the gold salts used are not efficacious in the treatment of experimental tuberculosis in guinea-pigs. No attempt has been made to use these salts in human patients and we have no wish to draw any unfavorable conclusions as to the efficacy of gold salts in the treatment of human tuberculosis. But the tendency to hemorrhage and hyperemia in the

gold treated animals and the marked shortening of life on account of the treatment certainly suggest that the treatment of human tuberculous patients with gold is not without danger. Furthermore, the chemical analyses of the organs demonstrate that there is no specific affinity of gold for tuberculous tissues and that the gold in the tissues is probably fixed in the tissue cells in such a form that it cannot inhibit the growth of the tubercle bacillus nor the development of the tubercle even when its concentration in the tissues is much more than sufficient to cause complete inhibition in the test tubes.

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